16715CPA

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: William J. Rea and
Serial No.: Bertie B. Griffiths
Filed: July 30, 1997

Attorney Docket: EHCD-16715-CPA2
Group Art Unit: 1644
Examiner: Schwadron, R.

For: **Autogenous Lymphatic Factor for Modification of T and B Lymphocyte Parameters**

TRANSMITTAL LETTER

Assistant Commissioner for Patents
Washington, DC 20231

Sir:

In response to the Office Action mailed January 8, 2003, attached is the Corrected Brief for Appellants as requested by the examiner.

The Commissioner of Patents and Trademarks is hereby authorized to charge any fees or overpayments to Deposit Account No. 03-3840. A duplicate copy of this fee authorization sheet is enclosed for this purpose.

Dated: January 27, 2003

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Respectfully submitted,

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In Re Application of: William J. Rea
and Bertie B. Griffiths

Attorney Docket: 16715/CPA2

Serial No. 08/902,692

Art Unit: 1644

Filed: July 30, 1997

Examiner: Schwadron, R.

For: **Autogenous Lymphatic Factor for Modification of T and B Lymphocyte Parameters**

CORRECTED BRIEF FOR APPELLANTS

Assistant Commissioner of Patents
Washington, D. C. 20231

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January 27, 2003

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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

In Re Application of: William J. Rea
and Bertie B. Griffiths

Attorney Docket: 16715CIP

Serial No. 08/902,692

Art Unit: 1644

Filed: July 30, 1997

Examiner: Schwadron, R.

For: **Autogenous Lymphatic Factor for Modification of T and B Lymphocyte Parameters**

CORRECTED BRIEF FOR APPELLANTS

Assistant Commissioner of Patents
Washington, D. C. 20231

Sir:

This is an appeal from the final Office Action mailed October 30, 2001 and the Advisory Action mailed February 21, 2002 in the above-identified application for patent.

A Notice of Appeal and fee, together with an Extension of Time Request and fee, was filed by Express Mail on April 25, 2002, which was acknowledged to have been actually received in the Patent and Trademark Office on April 29, 2002.

A copy of the claims involved in the appeal is attached as Appendix A.

Copies of the two references applied in the final Office Action against the pending claims are attached as Appendix B and C for convenient reference.

This brief is also supported by the "Supplemental Declaration of Vernon E. Scholes, Ph.D.," submitted on December 17, 2001 and considered and entered by the Advisory Action mailed February 21, 2002. A copy of the Declaration is attached as Appendix D for convenient reference.

This Brief for Appellants is being filed in triplicate, including the attached Appendixes, and is accompanied by the requisite fee set forth in 37 C.F.R. § 1.17(c), together with an Extension of Time Request and fee, all by Express Mail.

I. REAL PARTY IN INTEREST

The real party in interest in this application is the named inventors, William J. Rea, Ph.D. and Bertie B. Griffiths, Ph.D., who are referred to herein as the Appellants or Applicants. The application is not assigned.

II. NO RELATED APPEALS OR INTERFERENCES

No other appeals or interferences are known to the Appellants or the Appellants' legal representative which would directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal. There is no assignee.

III. STATUS OF CLAIMS

Claims 1-7, 20, 22-31, 33-39 have been canceled. Claims 8-19, 21, 32, 40-48 have been withdrawn from consideration as being drawn to non-elected inventions. Claims 49-66 are pending in the application.

Applicants are appealing the final rejection of pending Claims 49-66. The pending claims, as amended, are set forth in "Appendix A." The precise wording of the claims on appeal appear in the file history as follows:

(a) Claims 49-50, 52-59 appear at pages 2-3 of the "Amendment" filed April 7, 1999;

(b) Claims 51 and Claims 60-64 appear at pages 2-3 of the "Preliminary Amendment" filed with a first "CPA" on December 20, 1999; and

(c) Claims 65-66 appear at page 1 of the "Preliminary Amendment" filed with a second "CPA" on September 11, 2000.

IV. STATUS OF AMENDMENTS

All requested amendments have been entered. Regarding amendments filed after the final Office Action mailed October 30, 2001, Applicants submitted the "Supplemental Declaration of Vernon E. Scholes, Ph.D." on December 17, 2001. The Advisory Action mailed February 21, 2002 stated that this last paper submitting the Supplemental Declaration would be entered.

V. SUMMARY OF INVENTION

Applicants' invention as claimed in the pending claims is directed to "a method of treating a chemically sensitive individual." Although Claims 49-66 are pending in the application and all the claims do not stand or fall together, Claim 49 is representative as a summary of the invention:

> 49. A method for treating a chemically sensitive individual comprising the steps of:
>
> (a) collecting a blood sample from the individual;
>
> (b) isolating mixed T and B lymphocytes from the blood sample;
>
> (c) propagating the isolated mixed T and B lymphocytes to obtain propagated lymphocytes;
>
> (d) lysing the propagated lymphocytes to obtain a lysate; and
>
> (e) administering the lysate to the individual.

The claimed method is supported by the specification, including the following general statement in the "Summary of Invention" section of the specification:

> According to the invention, autogenous lymphocytic factor (ALF) is a substance derived from an individual's own normal T and B lymphocytes isolated from a blood sample and then *propagated in culture*. The ALF if then administered to the same individual. . . . According to one aspect of the invention, the ALF for the clinical treatment is in the form of *a lysate prepared from normal mixed T and B lymphocytes grown in cell culture*. For example, according to one embodiment of the invention, *the lysate is prepared from the cell cultures of isolated T lymphocytes or B lymphocytes*. According to yet another embodiment of the invention, *the lysate is prepared from the cell cultures of one or more isolated subclasses of blood lymphocytes*, for example, the T_4 or T_8 lymphocytes, of any combination of the lymphocytes subclasses. According to another aspect of the invention, the ALF comprises one or more enzymes isolated from *a lysate prepared from lymphocytes grown in cell culture*.

Specification at page 3, lines 7-21 (*emphasis added*).

"The presently preferred embodiment of the method for preparing the invention involves collecting blood from the ill individual and ***growing the normal lymphocytes in culture, harvesting the propagated cells***, and collecting the biological regulator (ALF) from the cells for use in clinical treatments. The following steps are used . . . ." Specification at page 8, lines 20-24 (*emphasis added*). In addition, the specification shows the order of magnitude of time required for cell growth: "FIG. 1 is a diagrammatic representation of a normal mammalian cell cycle, wherein *the overall cell*

doubling time is about 20 - 24 hours . . . ." Specification at page 5, lines 13-15 (*emphasis added*). Accordingly, the specification at pages 8-10 discloses that the culture is "*monitored daily* until yield is approximately 5-8 x 10^6 cells per ml." Specification at page 9, lines 19-20 (*emphasis added*). Furthermore, in the "Clinical Testing and Results" section of the specification, it states: "In general, treatment with autogenous lymphocytic factor (ALF) is accomplished by separating the patient's own T and B lymphocytes and growing them in cell cultures. *This process takes approximately six weeks.* After there are sufficient and robust lymphocytes, they are fractured mechanically, and the immunity factors are removed, sterilized, and standardized. . . . ." Specification, page 15, lines 14-18 *(emphasis added)*.

VI. ISSUES

The technically-stated issues presented for review in this appeal are:

(1) Whether Claims 49-66 are unpatentable under 35 U.S.C. § 103(a) as being obvious over Youdim et al. in view of Warren (U.S. Patent No. 4,435, 384);

(2) Whether Claims 65-66 are unpatentable under 35 U.S.C. § 112, first paragraph, for lacking support in the specification as originally filed for the language "isolating mixed T and B lymphocytes from the blood sample, which includes at least some normal T and B lymphocytes"; and

(3) Whether Claims 65-66 are unpatentable under 35 U.S.C. § 112, second paragraph, as being indefinite in the recitation of "normal T and B lymphocytes".

VII. GROUPING OF CLAIMS

Appellants state that all the claims do not stand and fall together, and request the following grouping of claims. In this section, Appellants briefly explain the requested grouping based on differences between the claims. In the argument section, Appellants explain why the claims of each group are believed to be separately patentable.

Independent Claim 49 is the most basic claim in the application. Claims 50-59 depend from Claim 49. The method of Claim 49 includes, among other things, the steps of "*propagating* the isolated mixed T and B lymphocytes [obtained from an individual] *to obtain propagated lymphocytes*" and "*administering the lysate [of the propagated lymphocytes] to the [same] individual.*" (*Emphasis added.*)

Dependent Claim 52 from Claim 49 defines that "*the step of propagating* the isolated mixed T and B lymphocytes *further comprises the steps of: culturing* the isolated mixed T and B lymphocytes *with a cell growth medium* at about 37°C." (*Emphasis added*). Dependent Claim 53 from Claim 52 further defines that "*the cell growth medium* is supplemented with bovine calf serum." (*Emphasis added*). Dependent Claim 54 also depends from Claim 52.

Independent Claim 60 is a more specific claim. For example, Claim 60 includes the step of propagating the isolated mixed T and B lymphocytes to obtain propagated lymphocytes by:

(i) *culturing the isolated mixed T and B lymphocytes with a cell growth medium* at about 37°C;

(ii) centrifuging the cultured lymphocytes;

(ii) removing the supernate from the centrifuged lymphocytes; and

(iv) washing the centrifuged lymphocytes in normal saline with further centrifugation to obtain the propagated lymphocytes."

(*Emphasis added*). Claims 61-64 depend from Claim 60. For example, Dependent Claim 61 from Claim 60 further defines that "*the cell growth medium* is supplemented with bovine calf serum." And dependent Claim 62 from Claim 60 further defines that "the culture is monitored until the yield is approximately 5-8 x 10^6 cells per ml."

Claim 65 is a third independent claim. The only difference between independent Claim 65 and independent Claim 49 is in the step of "isolating mixed T and B lymphocytes from the blood sample, *which includes at least some normal T and B lymphocytes.*" (*Emphasis added*).

Claim 66 depends from Claim 65. Dependent Claim 66 further defines that "*the step of propagating* the isolated mixed T and B lymphocytes *further comprises the step of culturing with cell growth medium* at 37°C for a sufficient time to obtain approximately 5-8 X 10^6 cells per ml. " (*Emphasis added*).

All the pending Claims 49-66 were rejected under 35 U.S.C. § 103(a), however, Claims 65-66 were additionally rejected under 35 U.S.C. § 112, first and second paragraphs.

Accordingly, for the limited purposes of this appeal, Applicants group and will argue the pending claims as follows:

Group I: Claims 49-51 and 55-59, and 65 stand or fall together on the issue of patentability under 35 U.S.C. § 103(a), and Applicants suggest that Claim 49 is representative of this group;

Group II: Claims 52-54, 60-64, and 66 stand or fall together on the issue of patentability under 35 U.S.C. § 103(a), which claims define the step of "propagating . . ." to further comprise or include the step of "culturing" and "with cell growth medium . . .", and Applicants suggest that Claim 52 is representative of this group;

Group III: Claims 65-66 stand or fall together on the issue of patentability under 35 U.S.C. § 112, first paragraph, and Applicants suggest that Claim 65 is representative of this group; and

Group IV: Claims 65-66 stand or fall together on the issue of patentability under 35 U.S.C. § 112, second paragraph, and Applicants suggest that Claim 65 is representative of this group.

VIII. ARGUMENT

A. The Prosecution History and Evidence of Record

Appellants believe that stating the prosecution history and the evidence of record would be the most appropriate approach to showing how the issues have been sharpened for appeal and reduce the effort that would otherwise be required in working through the lengthy prosecution history.

1. The Claims Involved in the Appeal

Claim 49 and dependent Claims 50-59 were first presented in the "Amendment" filed April 7, 1999. Claim 49 has not been amended since it was first presented:

49. A method for treating a chemically sensitive individual comprising the steps of:
    (a) collecting a blood sample from the individual;
    (b) isolating mixed T and B lymphocytes from the blood sample;
    (c) propagating the isolated mixed T and B lymphocytes to obtain propagated lymphocytes;
    (d) lysing the propagated lymphocytes to obtain a lysate; and
    (e) administering the lysate to the individual.

Thus, the method of Claim 49 includes, among other things, the steps of "*propagating* the isolated mixed T and B lymphocytes [obtained from an individual] *to obtain propagated lymphocytes*" and "*administering the lysate [of the propagated lymphocytes] to the individual.*" (*Emphasis added.*)

Claims 50-59 depend from Claim 49. Dependent Claim 52 from Claim 49 defines that "*the step of propagating* the isolated mixed T and B lymphocytes *further comprises the steps of: culturing* the isolated mixed T and B lymphocytes *with a cell growth medium* at about 37°C." (*Emphasis added*). Dependent Claim 53 from Claim 52 further defines that "*the cell growth medium* is supplemented with bovine calf serum." (*Emphasis added*). Dependent Claim 54 also depends from Claim 52.

Claims 60-64 were first presented for consideration at pages 2-3 of the "Preliminary Amendment" filed with a first "CPA" application on December 20, 1999. These additional claims were presented, in part, to help further focus the issues and differences between the Applicants and the Examiner. Claim 60 is an independent claim. It is a more specific claim including more of the particulars of the laboratory procedure described at pages 8-10 of the specification. Claims 61-64 depend from Claim 60.

Claims 65-66 appear at page 1 of the "Preliminary Amendment" filed with a second "CPA" on September 11, 2000. Again, these additional claims were presented, in part, to help further focus the issues and differences of opinion between the Applicants and the Examiner. Claim 65 is an independent claim. The only difference between independent Claim 65 and independent Claim 49 is in the step of "isolating mixed T and B lymphocytes from the blood sample, *which includes at least some normal T and B lymphocytes*." (*Emphasis added*).

Claim 66 depends from Claim 65. Dependent Claim 66 further defines that "*the step of propagating* the isolated mixed T and B lymphocytes *further comprises the step of culturing with cell growth medium* at 37°C for a sufficient time to obtain approximately 5-8 X 10^6 cells per ml. " (*Emphasis added*).

2. The Rejection Arguments

The final Office Action mailed October 30, 2001 rejected all the pending Claims 49-66 [Appendix A] under 35 U.S.C. 103(a) as being unpatentable over Youdim et al. [Appendix B] in view of Warren (US Patent 4,435,384) [Appendix C]. It is noteworthy the Youdim et al. is actually a publication of the same Dr. Rea that is one of the inventors of this application for patent. The rejection argument, at Paragraph 6 at pages 3-4, was substantially copied by the Examiner from the same argument elaborated in several previous Office Actions:

> Youdim et al. teach the treatment of "environmentally sensitive patients" with transfer factor (see entire document). The transfer factor is prepared from lysed

leukocytes (see page 56, first column). It appears that these "environmentally sensitive patients" would be encompassed by the term "chemically sensitive individual". Youdim et al. do not teach that the transfer factor was produced from autologous blood cells as per claim [sic] the claimed invention. Warren teaches that transfer factor can be obtained from the lymphocytes of any individual as long [sic] the donor has no history of recurrent infection by herpes virus (see column 2). Therefore a routineer would have used any source of lymphocytes, including autologous, for preparing the transfer factor for use in the method taught by Youdim et al. Youdim et al. do not teach that the transfer factor was produced using the particular steps recited in the claimed method. Warren teaches that transfer factor can be produced by a variety of different methods and lists one particular method (see columns 2 and 3). The steps recited in the claimed method are art known procedures that would be expected to yield a lysate containing transfer factor. Regarding the use of "mixed T and B lymphocytes", Warren teaches that transfer factor is produced from lymphocytes (see column 2). The cells used in the method taught by Warren are propagated in that they are cultured in vitro. The use of commercially available density gradients such as FICOLL to separate lymphocytes is well known in the art. Warren teaches the use of heparinized tubes to collect the blood sample. Warren teaches 37 degree incubation of lymphocytes (see column 2). Youdim et al. teaches subcutaneous administration of transfer factor (see page 56, column 2). Youdim et al. teaches multiple administration of transfer factor (see page 56, column 2). Youdim et al. teaches that skin testing (eg. DTH) can be used to measure the response to transfer factor. It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to have created the claimed invention because Youdim et al. teach the treatment of "environmentally sensitive patients" with transfer factor, Warren teaches that transfer factor can be obtained from lymphocytes of any individual as long as the donor has no history of recurrent infection by herpes virus, and the preparation recited in the claims appears to be transfer factor made by a method that uses art known techniques that would have been obvious to use to prepare transfer factor.

Regarding applicants comments about culture and propagation, there is currently no limitation in the claims under consideration that states that the cells are cultured for any defined period of time. Regarding the term "propagation", said term in itself does not specify any particular time period of in vitro culture. In fact, Steadmans Medical Dictionary, 24th Edition indicates that the term "propagate" can be defined as "to generate". Thus, the term propagation does not necessarily imply any particular period of culture. Regarding the limitation of claims 66 and 62, the starting concentration of cells used in the claimed method is not specified. Thus, if the cells were initially at the concentration specified in claim 66 or 62, then they would not require any particular time period to achieve the concentration recited in claim 62 or 66. Said limitation would only take on meaning if the initial concentration of cells was specified and if the concentration was such that it would take a particular time period of culture to achieve the concentration recited in claims 66 or 62. Applicants arguments involve limitations currently not recited in the claims under consideration.

The final Office Action mailed October 30, 2001 additionally rejected Claims 65 and 66 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention for the reasons elaborated in the previous Office Action. The rejection argument, at Paragraph 3, page 2, was substantially copied by the Examiner from the same argument previously elaborated:

> There is no support in the specification as originally filed for the method of claim 65 which recites "which includes at least some normal T and B lymphocytes". There is no written description of the scope of the claimed invention in the specification as originally filed (eg. the claimed invention constitutes new matter).
>
> Regarding applicants comments, there is no support in the specification as originally filed for the method of claim 65 which recites "which includes at least some normal T and B lymphocytes". There is no disclosure of said limitation in the method described in pages 9 and 10 of the specification.

The final Office Action mailed October 30, 2001 also rejected Claims 65 and 66 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The rejection argument, at Paragraph 4, pages 2-3, was substantially copied by the Examiner from the same argument previously elaborated:

> Claim 65 is indefinite in the recitation of "normal T and B lymphocytes" because it is unclear what this term means or encompasses. It is unclear as to what parameters distinguish a normal lymphocyte from an abnormal lymphocyte. The meaning of said term is not disclosed in the specification and it has no art recognized meaning.

3. The Responsive Arguments of Record

Claims 49-64 were at first and repeatedly rejected under 35 U.S.C. § 112, first paragraph, *for NOT reciting the use of "normal"* lymphocytes in these claims. See Office Action mailed September 29, 2000 at paragraph 4, page 2; Office Action mailed March 9, 2000 at paragraph 5, page 2; and Office Action mailed June 18, 1999 at paragraph 5, pages 3-4.

Applicants finally added Claims 65 and 66 to highlight the difference between claims with and without the use of the word "normal" lymphocytes. See "Preliminary Amendment" filed with the second "CPA" on September 11, 2000; compare Claim 49 to Claim 65 in Appendix A. The Examiner then also rejected the new Claims 65 and 66 under 35 U.S.C. § 112, both first and second

paragraphs, *but in this case for reciting the use of "normal"* lymphocytes. See Office Action mailed September 29, 2000, at page 3.

Because Applicants and Examiner have gone round and round, including on the meaning of the term "normal" as used in the application, Applicants believe it would be helpful to now restate on appeal the following argument from the "Response to Office Action" filed March 29, 2001:

> The Examiner's continued attention to the application is appreciated. Both sides have gone round and round over certain issues. Both sides seem annoyed and frustrated.
>
> As suggested by the Examiner, several months ago the Applicants asked an expert in the field to review the application for the purpose of submitting additional evidence in the record as to how a person of skill in the art would interpret some of the language used in the specification. Unfortunately, the expert has been suffering from severe back pain and recently had major back surgery. After the expert recovers sufficiently to continue working on the matter, Applicants plan to submit such evidence.
>
> Meanwhile, the Applicants request the Examiner to take a step back and, if possible, reconsider the impasse. This might save both sides a lot of time and trouble.
>
> Claims 49-66 were rejected under 35 U.S.C. § 112, first paragraph. Claims 65 and 66 were also rejected under 35 U.S.C. § 112, second paragraph.
>
> The steps 1-15 of the preferred procedure according to the invention for making "ALF" are described at pages 9-10 of the specification. Both sides appear to agree that this detailed and complete procedure is clear to persons skilled in the art.
>
> Furthermore, general statements in an application regarding an invention should be construed to cover the preferred procedure. For example, the general statement that "The preferred embodiment of the method for preparing the invention involves collecting blood from the ill individual and growing the normal lymphocytes in culture, harvesting the propagated cells, and collecting the biological regulator (ALF) from the cells for use in clinical treatments" at the bottom of page 8 of the specification is specifically directed to the following steps 1-15 of the preferred procedure according to the invention. As a starting point, any interpretation of the general steps, including the step of "growing the normal lymphocytes in culture" should be made consistent with the specific steps 1-15 of the preferred procedure.
>
> The Examiner's prior interpretation of this general language would seem to require something more or different than what is described in steps 1-15 of the preferred procedure. In particular, a claim reciting the use of "normal" lymphocytes would arguably require some additional separation step, which is not described in steps 1-15 of the preferred procedure described at pages 9-10 of the specification. Applicants do not understand, for example, what part of Claim 49, steps (a)-(e) is not supported or described by steps 1-15 of the preferred procedure described at pages 9-10 of the specification.
>
> A premise of the invention is that even an ill person will have some normal lymphocytes included in the one or more isolated "lymphocytic layers" obtained from the person's blood sample. For example, the originally-filed specification at page 6,

line 9-10, discloses "preparing ALF from the patient's own normal (non-cancerous or otherwise dysfunctional) lymphocytes." The specification also discusses normal and abnormal functioning lymphocytic cells by reference to the lymphocytic cell cycle. This is a measure based on a number of cells in the aggregate, not the appearance of a single cell.

The Examiner also rejected Claim 65, which was presented to help clarify this premise of the invention by including the step of "isolating mixed T and B lymphocytes from the blood sample, which includes at least some normal T and B lymphocytes." But this was rejected as being new matter, despite the statements in the originally-filed application about the normal "preparing ALF from the patient's own normal (non-cancerous or otherwise dysfunctional) lymphocytes" and despite the steps 1-15 of the preferred procedure according to the invention. Applicants do not believe this is a fair or proper interpretation of their application.

Claims 49-66 were also rejected under 35 U.S.C. § 103(a) as being unpatentable over Youdim et al. in view of Warren. Neither Youdim nor Warren teach or suggest propagation of the cells. By any meaningful definition, one cannot propagate lymphocytes by "incubation" at 37 degrees for 20 minutes and without any culture medium. As would be appreciated by a person of skill in the art, Warren is actually disclosing a separation step, not a cell propagation step. By any meaningful definition or standard whatsoever, Warren does not teach or suggest any propagation of lymphocytic cells.

4. The Supplemental Declaration of Vernon E. Scholes, Ph.D.

The Examiner appears to have gone out of his way to give Applicants a procedural opportunity to supplement the evidentiary record for appeal with an appropriate expert declaration, as Applicants had indicated they would like to do.[1] For this, Applicants are appreciative.

Once the expert had sufficiently recovered from his back surgery, Applicants obtained a "Declaration of Vernon E. Scholes, Ph.D.," which was filed on August 14, 2001 with an Extension of Time Request and fee. Although the final Office Action mailed October 30, 2001 technically refused to consider the Declaration, the Examiner said he would consider and enter the Declaration if a technical deficiency was corrected:

> Regarding applicants comments about the Scholes declaration, said declaration lacks a listing of publications from Scholes. In the absence of a list of Scholes' publications it is unclear as to whether Scholes actually is an expert in the subject matter under consideration. The Scholes declaration will be considered upon receipt of the aforementioned information.

---

[1] See Office Action mailed June 15, 2001 (giving Applicant time to supplement its previous bona fide attempts to reply); and final Office Action mailed October 30, 2001 (giving Applicant an opportunity to supplement the first-filed declaration of Scholes to further establish the credentials of the expert.)

Accordingly, Applicants later filed a Supplemental Declaration of Vernon E. Scholes, Ph.D. The only differences between the original Declaration and the Supplemental Declaration were: (a) the title was changed to add the word "supplemental"; (b) under the subheading "Expert Qualifications," a list of extensive publications was referred to and attached as Exhibit B thereto to overcome the Examiner's refusal to consider the Declaration in the final Office Action mailed October 30, 2001; and the last paragraph was changed to better comply with the requirements of 18 U.S.C. § 1001. A copy of the Supplemental Declaration of Vernon E. Scholes, Ph.D. is attached as Appendix D.

Although a copy is attached, Applicants substantially reproduce it below (with original emphasis), as it did with the Examiner's and Applicants' arguments of record, which presentation format is believed will be most helpful to understanding the formation of the issues in this appeal:

> Expert Qualifications and Experience
>
> I earned a Ph.D. in Medical Microbiology at the University of Kansas, Lawrence, Kansas.
>
> My qualifications and experience include having been a Professor of Microbiology and/or Immunology at several universities. I have taught courses in microbiology, immunology, cell biology, botany, virology, mycology, parasitology, and medical technology at undergraduate, graduate, medical, and dental schools. I have performed research in the areas of immunobiology (AIDS and cancer), virology, microbiology, and botany; have directed the research of 11 M.S. students, 10 Ph.D. students, and 4 Post-doctoral students; and have written and/or presented over 60 research papers, abstracts, and presentations. I have set up 2 flow cytometry laboratories and pioneered development of immunological and cell cycle analysis using the flow cytometer. In addition, I have been an invited participant in 7 conferences of the Society for Analytical Cytology. I continue to be an independent Immunology/Microbiology Consultant.
>
> A true and correct copy of my latest curriculum vitae is attached hereto as Exhibit A.
>
> A true and correct list of my "Publications, Presentations, and Abstracts," and "Special Symposia and Consultantships" and list of the M.S. Theses, Ph.D. Dissertations, and Post-Doctoral Works that I have directed is attached hereto as Exhibit B.
>
> Scope of Review
>
> Dr. Rea and Dr. Griffiths requested my independent review of their application for patent, which I understand was filed with the United States Patent and Trademark Office on July 30, 1997 and further identified as U.S. application serial number 08/902,692.
>
> In particular, I was provided with a copy of the following papers from the application file history:

a) application entitled "Autogenous Lymphocytic Factor for Modification of T and B Lymphocyte Parameters";
b) an "Amendment" to the application dated April 7, 1999;
c) a further "Preliminary Amendment" to the application dated December 20, 1999;
d) a second "Preliminary Amendment" to the application dated September 11, 2000; and
e) an "Office Action" dated September 29, 2000, together with the references cited against the application, Youdim et al. (Clinical Ecology, Volume 7, Number 3) and Warren (U.S. Patent No. 4,535,384).

I was requested to provide my independent expert opinion regarding the issues raised by these papers, including:

a) the meaning of "normal" lymphocytes, in the context of how the term was used in the application;
b) whether the invention as disclosed in the application requires any separation of "normal" lymphocytes from other lymphocytes prior to the propagation of the lymphocytes;
c) whether Youdim et al. discloses any teaching or suggestion of making autologous lymphocytes factor (ALF); and
d) whether Warren discloses any teaching or suggestion of propagating cells or making autologous lymphocytes factor (ALF; and
e) whether the hypothetical combination of Youdim et al. and Warren would render obvious the general methods of Applicant's invention, as defined in Claim 49 and exemplified by the particular preparation steps set forth at pages 8-10 and the following treatment steps and clinical testing.

"Normal" Means Normal-Functioning Lymphocytes

"Normal" to a pathologist would more likely refer to normal-appearing or normal in appearance, whereas "normal", to an immunologist, like myself, would refer to normal-functioning lymphocytes. There is a great difference between normal in appearance and normal in function. Normal appearing lymphocytes to a pathologist may not be "normal" functioning lymphocytes. That is, a patient suffering from immune deregulation may have normal appearing but not normal functioning lymphocytes.

One example of immune deregulation is shown in the histogram analysis as described in the original submission of the invention. In DNA analysis, normal functioning lymphocytes would have approximately 90% of the lymphocytes in the G_0/G_1 phases of the cell cycle, as illustrated in Figure 1 and by representative sample DNA measurements of normal or control volunteers shown in Figures 2a and 2b of the application. In contrast, deregulated lymphocytes would tend have approximately 10-15% of the lymphocytes in the G_0/G_1 phases and 85-90% in the S/G_2M phases, as illustrated and best shown by the representative sample DNA measurements of environmentally compromised individuals shown in Figures 3a, 3b, and 3c, especially Figures 3b and 3c.

Furthermore, as used in the disclosure of the invention, the functioning of the lymphocytes, whether "normal" or deregulated, is analyzed using an aggregate of cells in a sample, not by looking at an individual cell.

The application itself indicated that "normal" refers to normal functioning cells. For example, the application refers to "the patient's own normal (non-cancerous or otherwise dysfunctional) lymphocytes. (Application, page 6, lines 9-10.) Perhaps it would have been better to state "normal functioning" lymphocytes rather than just "normal" in the body of the submission, however, in the full context of the disclosure, the use of the term "normal" is clearly directed to normal functioning cells, especially as would be indicated by DNA analysis.

No Separation of "Normal" Lymphocytes Prior to Propagation Is Required

According to the example of the preparation of ALF described at pages 8-10 of the application, there is no step of any separation of "normal" lymphocytes from abnormal or deregulated lymphocytes prior to the propagation step.

Furthermore, even in a patient suffering from immune deregulation, especially where environmental factors such as a chemical sensitivity contribute to the deregulation, at least some portion of the lymphocytic cells would be expected to be either normal functioning or capable of normal functioning under healthier conditions, i.e., when the incitant to the deregulation is removed. It should be understood from the context of the disclosure in the application, especially the lack of any separation step in the example, that, under culturing conditions, ideal for lymphocytic cell growth and propagation, normal functioning cells in the lymphocytic sample would be readily propagated. The purpose of the propagation step is to produce abundant numbers of robust, normal functioning lymphocyte cells from a patient's own normal lymphocyte cells that are either normal functioning or capable of normal functioning under healthier conditions.

Youdim et al. Does Not Disclose or Suggest Propagating Cells or Autologous Factor (ALF)

Youdim et al. does not disclose or suggest propagating or culturing cells to obtain abundant numbers of healthy lymphocytes. For example, the publication of Youdim et al. (pg. 56, line 4) notes that the lymphocytes were "pooled" from random normal healthy donors (line 2). At the time of the Youdim publication, it was still a common practice in the art to use "pooled" lymphocytes, e.g., lymphocytes from a large number of donors in order to obtain sufficient numbers of lymphocytes from which to extract sufficient "transfer factor" (TF). Environmentally sensitive patients refers to the patient being treatment with TF, not the persons from which the TF was obtained. For example, Youdim specified "Peripheral blood from random normal health donors." There is no teaching or suggestion in Youdim that TF was produced from "autogenous blood cells." This is an important difference between Youdim et al. and the application of Drs. Griffiths and Rea, i.e., Youdim et al. used blood from random healthy donors. Griffiths and Rea used autogenous lymphocytes.

Warren Does Not Disclose or Suggest Propagating Cells or Autologous Factor (ALF)

Warren includes the statement "the incubation of the syringe and contents for 20 min. at 37° C" at column 2, lines 60-64. This "incubation" time of 20 minutes would not be for propagation of cells because the generation time of the cells would

be approximately 20 hours or more. In fact, the "incubation" time of 20 min. at 37° C is to remove the macrophage type cells by giving them sufficient time to adhere to the "cotton wool" and not for propagation. This procedure for the removal of macrophage type cells is well known to those skilled in this art.

In contrast, the "propagation" of cells would be understood by a person of ordinary skill in the art to require sufficient generation time for the increase in the number of cells.

Also, in my more than 30 years practicing this art, I have never heard of using "cotton wool" for this procedure but instead using glass wool fibers as described by Warren in column 3, line 68. I fear Warren did not carefully edit his submission, since he states using "cotton wool" in column 2, lines 55-56, and glass wool in column 3, line 68.

Furthermore, Warren also taught the use of pooled lymphocytes from healthy donors. Warren's description of a "preferred embodiment" in which he described preparation of lymphocytes was on a "pilot plant scale" (as would be described in industrial language) and in column 3, lines 63-66 he described the preparation on a "production scale" (scale-up technique) thereby producing sufficient numbers of lymphocytes from which to extract TF in quantities sufficient to include in his composition for skin treatments. According to Warren's patent, a routineer would have to use large numbers of lymphocytes "prepared by utilizing 'scale-up techniques' of the procedure outlined above which permit purification of large numbers of lymphocytes" as described in column 3, lines 63-66. This is why Warren was so emphatic about using lymphocytes from suitable donors; i.e., donors having no history of recurring infection by herpes virus (Warren column 2, lines 35-37). (Of course, Warren's patent was filed April 30, 1982 prior to the AIDS epidemic.) Warren's method is different from that of Drs. Rea and Griffiths in that Warren used blood from healthy donors while Rea and Griffiths used autologous lymphocytes.

Invention Not Obvious Based on Hypothetical Combination of Youdim et al. and Warren

My understanding is that the claimed invention in the application of Rea and Griffiths is defined and illustrated by the following pending claim:

Claim 49: A method for treating a chemically sensitive individual comprising the steps of:

(a) collecting a blood sample from the individual;
(b) isolating mixed T and B lymphocytes from the blood sample;
(c) propagating the isolated mixed T and B lymphocytes to obtain propagated lymphocytes;
(d) lysing the propagated lymphocytes to obtain a lysate; and
(e) administering the lysate to the individual.

In my opinion, these basic steps are fully supported by the written description and figures of the application, and should not be interpreted by a person of ordinary skill in the art to require any separation of "normal" lymphocytes from abnormal or deregulated lymphocytes prior to the propagation step.

Rea and Griffiths are using a technique of cell culture (propagation) of lymphocytes to produce sufficient numbers of normal functioning lymphocytes from which to extract quantities of ALF sufficient to use in replacement of insufficient

concentrations of ALF in patients immunologically deregulated or replacement of ALF to stimulate an immunologically deregulated patient to proper regulation.

Based on the foregoing, in my opinion, the hypothetical combination of Youdim et al. and Warren does not teach or suggest the invention as defined by Claim 49 and as set forth in the written description of the invention, including the specific, illustrative example procedure set forth at pages 8-10 of the application and the following treatments steps and clinical testing.

5. The Advisory Action After Final

The Advisory Action mailed February 21, 2002, stated that "The affidavit, exhibit or request for reconsideration has been considered but does not overcome the rejection because the pending claims are rejected for the reasons elaborated in the previous Office Action. Also see enclosed note." The enclosed note is reproduced below:

> Regarding the Scholes declaration, said declaration does not clarify what "normal T and B lymphocytes" means or encompasses. In fact, said declaration actually indicates that said term could potentially be interpreted in a variety of different ways (eg. normal in appearance versus normal in function). Furthermore, the claims do not recite the limitation "normal functioning". Even if the claims did recite said limitation, it would be unclear as to what "normal functioning" means or encompasses. For example, what parameters are encompassed by "normal functioning" versus "abnormal functioning" of T and B cells. Regarding Scholes comments about "propagation", Steadmans Medical dictionary, 24th edition indicates that "propagate" means "to generate". Thus, the term propagate does not imply any particular period of culture.

6. Impasse and Issues on Appeal

While Applicants overcame certain rejections of the claims, having reached an impasse with the Examiner on the remaining issues, Applicants appealed the final rejections. For example, either based on the Applicants' arguments filed on March 29, 2001 and/or the Scholes Declaration, the final Office Action mailed October 30, 2001, finally relented on the rejections of Claims 49-64 under 35 U.S.C. 112, first and second paragraphs, which claims do not recite the use of "normal" lymphocytes. However, the final Office Action maintained the following three issues for appeal:

(1) Whether Claims 49-66 are unpatentable under 35 U.S.C. § 103(a) as being obvious over Youdim et al. in view of Warren (U.S. Patent No. 4,435, 384);

(2) Whether Claims 65-66 are unpatentable under 35 U.S.C. § 112, ¶ 1, for lacking support in the specification as originally filed for the language "isolating mixed T and B lymphocytes from the blood sample, which includes at least some normal T and B lymphocytes"; and

(3) Whether Claims 65-66 are unpatentable under 35 U.S.C. § 112, ¶ 2, as being indefinite in the recitation of "normal T and B lymphocytes".

Each of these issues is separately discussed in more detail below.

B. Claims 49-66 Are Not Obvious Over Youdim et al. in view of Warren

The final rejection acknowledged that: "Youdim et al. do not teach that the transfer factor was produced from autologous blood cells as per claim [sic] the claimed invention." Final Office Action mailed October 30, 2001, p. 3. The rejection also acknowledged that: "Youdim et al. do not teach that the transfer factor was produced using the particular steps recited in the claimed method." Final Office Action, p. 4. While all the steps of the claimed procedure as a whole relate to the "autologous" nature of the method, the issue regarding the "particular steps recited in the claimed method" turn on the proper interpretation of the claimed step of "propagating the isolated mixed T and B lymphocytes to obtain propagated lymphocytes." The final Office Action rejected all the pending Claims 49-66 [Appendix A] under 35 U.S.C. 103(a) as being unpatentable over Youdim et al. [Appendix B] in view of Warren (US Patent 4,435,384) [Appendix C]. It is noteworthy that Youdim et al. is actually a publication of the same Dr. Rea that is one of the inventors of this application for patent. To make this alleged combination, the rejection made five specific errors regarding the disclosure in Warren.

(1) The final Office Action stated that: "Warren teaches that transfer factor can be obtained from the lymphocytes of any individual as long [sic] the donor has no history of recurrent infection by herpes virus (see column 2). Therefore a routineer would have used any source of lymphocytes, including autologous, for preparing the transfer factor for use in the method taught by Youdim et al." Final Office Action, pages 3-4. Warren, however, taught the use of pooled lymphocytes from healthy donors. The concept of using a "donor" or "pooled lymphocytes" from donors who have "no history of recurrent infection by herpes virus" does not teach or suggest including autologous. As described in the Scholes Declaration: "According to Warren's patent, a routineer would have to use large numbers of lymphocytes "prepared by utilizing 'scale-up techniques' of the procedure outlined above which permit purification of large numbers of lymphocytes" as described in column 3, lines 63-66. This is why Warren was so emphatic about using lymphocytes from suitable donors; i.e., donors having no history of recurring infection by herpes virus (Warren column 2, lines 35-37)." Appendix B, Supplemental Declaration of Vernon E. Scholes, p. 4. Warren does not teach

or suggest the concept of using "any source of lymphocytes, including autologous" as overstated in the rejection.

(2) The final Office Action stated that: "Warren teaches that transfer factor can be produced by a variety of different methods and lists one particular method (see columns 2 and 3). . . ." Final Office Action mailed October 30, 2001, pages 3-4. This overstates Warren, which actually states, in pertinent part: "The transfer factor may be prepared as documented in the medial literature. For example, detailed preparation of transfer factor described in . . . . The procedure I described therein for production of crude transfer factor is set forth as follows for convenience. . . ." Warren, Column 2, lines 39-47. In fact, Warren only discloses a single method for making "crude transfer factor," not "a variety of different methods" as overstated in the rejection.

(3) The final Office Action stated that: "Warren teaches 37 degree incubation of lymphocytes (see column 2). . . ." Final Office Action mailed October 30, 2001, pages 3-4. However, Warren actually discloses a separation step, not a cell propagation step. For example, Warren discloses a duration of only 20 minutes and a complete absence of any culture medium. Warren, Column 2, lines 48-68. The steps and conditions disclosed in Warren do not disclose a step of "propagating . . . to obtain propagated lymphocytes."

(4) The final Office Action appears to impose an unreasonable interpretation of this claim language to be so broad as to include Warren's procedure for mere filtration of lymphocytes. In this regard, the final Office Action argued that: "Regarding Scholes comments about 'propagation', Steadmans Medical dictionary, 24th edition indicates that 'propagate' means 'to generate'. Thus, the term propagate does not imply any particular period of culture." Final Office Action mailed October 30, 2001, pages 3-4. The reliance on Steadmans' Medical Dictionary in the rejection is misplaced. As discussed above, Warren does not disclose "any particular period of culture" because it does not disclose "culturing" whatsoever, merely a separation step involving "37 degree incubation" for only 20 minutes in the absence of any culture medium. Furthermore, Applicants' specification states that these lymphocyte cells have a cell cycle of approximately 20-24 hours under ideal cell culturing conditions. Specification at page 5, lines 13-15. Accordingly, the specification at pages 8-10 further discloses that the culture is "monitored daily until yield is approximately 5-8 x 10^6 cells per ml." Specification at page 9, lines 19-20. Furthermore, in the "Clinical Testing and Results" section of the specification, it states: "In general, treatment with autogenous lymphocytic factor (ALF) is accomplished by separating the patient's own T and B lymphocytes and growing them in cell

cultures. *This process takes approximately six weeks.* After there are sufficient and robust lymphocytes, they are fractured mechanically, and the immunity factors are removed, sterilized, and standardized. . . . ." Specification, page 15, lines 14-18 *(emphasis added)*. In the full context of the Applicants' disclosure, the claimed step of "propagation . . ." of cells would be understood by a person of ordinary skill in the art to require sufficient generation time for the increase in the number of cells. Appendix B, Supplemental Declaration of Vernon E. Scholes, p. 4.

(5) Furthermore, the argument in the Office Action regarding the interpretation of the step of "propagating . . ." fails to consider the problem that the inventor was attempting to solve and that the an applicant is entitled to be his own lexicographer. In construing claims, the problem the inventor was attempting to solve is a relevant consideration. *CVI/Beta Ventures, Inc. v. Tura LP*, 112 F.3d 1146, 1160, 42 U.S.P.Q.2d 1577, 1587 (Fed. Cir. 1997). The specification may expressly define terms used in the claims or define terms by implication. *Markman v. Westview Instruments, Inc.*, 52 F.3d 967, 979, 34 U.S.P.Q.2d 1321, 1330 (Fed. Cir. 1996, en banc), *aff'd,* 517 U.S. 370 (1996). The specification is generally dispositive and "is the single best guide to the meaning of a disputed claim term." *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582, 39 U.S.P.Q.2d 1573, 1577 (Fed. Cir. 1996). The purpose of the invention, as supported by the disclosed laboratory procedure, is to obtain abundant numbers of healthy lymphocytes. It is respectfully argued that the claim language requires more than mere "incubation" at 37 degrees for 20 minutes for a filtration procedure in the absence of any culture medium, which would not be understood to be "propagating" or "culturing" conditions and would not be expected to propagate (or generate) abundant numbers of healthy lymphocytes from a small sample of the patient's blood.

For each of these reasons, including the reasons stated in the Scholes Declaration, the hypothetical combination of Youdim et al. with Warren does not teach or suggest the invention as defined by representative Claim 49 of Group I. Thus, the hypothetical combination of Youdim et al. and Warren would fail to teach or suggest Applicants' invention as claimed, including the idea of using autologous lymphocytes and the step of propagating the lymphocytes. Appendix B, Supplemental Declaration of Vernon E. Scholes, pages 4-5.

C. Claims 52-54, 60-64, and 66 Are Separately Patentable and Not Obvious

While the final Office Action mailed October 30, 2001 rejected all the Claims 49-66 for the same reasons, Applicants assert that Claims 52-54, 60-64, and 66 (i.e., Group II) are patentable for

all the same reasons discussed above and are separately patentable for one additional reason. These claims of Group II define the step of "propagating . . ." to further specifically comprise or include the step of "culturing" the lymphocytes "with cell growth medium . . . ." The final Office Action glossed over the further limitations of these claims.

To the extent the final Office Action rejected the claims based on an erroneous and overbroad interpretation of the claimed step of "propagating . . . to obtain propagated lymphocytes" (i.e., an interpretation that is so overbroad as to include mere filtration of lymphocytes), the language of Claims 52-54, 60-64, and 66 define the step of "propagating . . ." to further specifically comprise or include the step of "culturing" the lymphocytes "with cell growth medium . . . ." Possibly recognizing that the combination of Youdim et al. and Warren fail to disclose the specifically-claimed step of "culturing" the lymphocytes "with cell growth medium," the final Office Action argued: "Warren teaches that transfer factor can be produced by a variety of different methods and lists one particular method (see columns 2 and 3). The steps recited in the claimed method are art known procedures that would be expected to yield a lysate containing transfer factor." Final Office Action mailed October 30, 2001, p. 4. As discussed above, however, Warren does not disclose "a variety of different methods" but only lists one particular method. An alleged combination rejection that does not teach or suggest the claimed invention is insufficient as a matter of law.

D. Claims 65-66 Are Supported by the Originally-Filed Specification

Claims 65-66 were presented during prosecution, in part, to help further focus the issues and differences of opinion between the Applicants and the Examiner. Claim 65 is an independent claim. The only difference between independent Claim 65 and independent Claim 49 is in the step of "isolating mixed T and B lymphocytes from the blood sample, *which includes at least some normal T and B lymphocytes*." (*Emphasis added*). The final Office Action stated: "There is no support in the specification as originally filed for the method of claim 65 which recites 'which includes at least some normal T and B lymphocytes'. There is no written description of the scope of the claimed invention in the specification as originally filed (eg. the claimed invention constitutes new matter). Final Office Action mailed October 30, 2001, p. 2.

The specification describes the subject matter defined by this claim by showing that the "isolated mixed T and B lymphocytes" are not subject to any further isolation steps to obtain "normal T and B lymphocytes." See Specification, pages 8-10. Furthermore, in the "Clinical Testing and

Results" section of the specification, it states: "In general, treatment with autogenous lymphocytic factor (ALF) is accomplished by separating the patient's own T and B lymphocytes and growing them in cell cultures. This process takes approximately six weeks. After there are sufficient and robust lymphocytes, they are fractured mechanically, and the immunity factors are removed, sterilized, and standardized. . . . ." Specification, page 15, lines 14-18 *(emphasis added)*. The same detailed description of the procedure at pages 8-10 of the specification also enables any person skilled in the art to make and use the subject matter defined by Claims 65-66 and sets forth the best mode contemplated by the inventors of carrying out the invention.

E. Claims 65-66 Do Not Include "Indefinite" Language

Again, Claims 65-66 were presented during prosecution, in part, to help further focus the issues and differences of opinion between the Applicants and the Examiner. Claim 65 is an independent claim. The only difference between independent Claim 65 and independent Claim 49 is in the step of "isolating mixed T and B lymphocytes from the blood sample, *which includes at least some normal T and B lymphocytes*." *(Emphasis added)*. The final Office Action stated: "Claim 65 is indefinite in the recitation of "normal T and B lymphocytes" because it is unclear what this term means or encompasses. It is unclear as to what parameters distinguish a normal lymphocyte from an abnormal lymphocyte. The meaning of said term is not disclosed in the specification and it has no art recognized meaning." Final Office Action mailed October 30, 2001, pp. 2-3. But after reviewing and discussing the specification in detail, the Scholes Declaration concluded:

> The application itself indicated that "normal" refers to normal functioning cells. For example, the application refers to "the patient's own normal (non-cancerous or otherwise dysfunctional) lymphocytes. (Application, page 6, lines 9-10.) Perhaps it would have been better to state "normal functioning" lymphocytes rather than just "normal" in the body of the submission, however, in the full context of the disclosure, the use of the term "normal" is clearly directed to normal functioning cells, especially as would be indicated by DNA analysis.

Scholes Declaration, pp. 2-3 (original emphasis). The specification includes a discussion of the use of DNA analysis to observe the functioning of the lymphocytic cell cycle, and the term is not indefinite to a person of skill in the art.

IX. REFERENCE TO APPENDIX

A copy of the claims involved in the appeal is attached as Appendix A.

A copy of Youdim, Rea, and Liang, "Treatment of Environmentally Sensitive Patients with Transfer Factor Part I: Immunologic Studies," *Clinical Ecology*, vol. 7, pp. 55-61, 1990, is attached as Appendix B.

A copy of Warren, U.S. Patent No. 4,435,384 issued March 6, 1984, is attached as Appendix C.

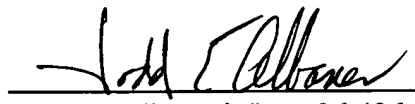
A copy of the "Supplemental Declaration of Vernon E. Scholes, Ph.D.," submitted on December 17, 2001 and considered and entered by the Advisory Action mailed February 21, 2002, is attached as Appendix D for convenient reference.

X. CONCLUSION

Based on the foregoing evidence, arguments, and authorities, it is respectfully requested that the rejection of Claims 49-66 under 35 U.S.C. § 103 and the rejections of Claims 65-66 under 35 U.S.C. § 112, first and second paragraph, all be reversed and the application be allowed for issue.

Dated: January 27, 2003

Respectfully submitted,



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